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Assessing the Percent of Necrosis after Neoadjuvant Chemotherapy with 24hr Infusional Cisplatin/3 Days Doxorubicin Intermittent with Ifosfamide-Doxorubicin for Osteosarcoma

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ABSTRACT

Introduction: osteosarcoma is the most common primary bone tumor in children and young adults and appropriate chemotherapy can increase limb sparing and overall survival. Yet, the toxicity of chemotherapy regimens including MTX can be life threatening. Therefore; we tried another chemotherapy regimen for these patients.

Method and materials: we investigated 15 patients aged 15 to 40 years old and used continuous infusion of cisplatin, doxorubicin intermittently with ifosfamide, doxorubicin as neoadjuvant chemotherapy. Percent of necrosis and toxicities was recorded for each patient.

Results: Out of 15 patients investigated, 13 were males and 2 females. Tumor necrosis≥ 90% (defined as good necrosis) was observed in 60% of patients. 26.7% of the patients showed leucopenia grade three or four, 26.7% had anemia grade three or four, and 20% showed thrombocytopenia grade three or four.

Conclusion: The above chemotherapy regimen can cause as good necrosis as the chemotherapy regimens including high dose of MTX with reduced toxicity and less nursing cares and laboratory tests. Of course small sample size limits extension of our result to all patients but trying this regimen is recommended in more patients to see more reliable results.

KEY WORDS: Osteosarcoma, Neoadjuvant chemotherapy, Necrosis

INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor in children and young adults.[1,2] Although in the past it was a lethal disease, achieving chemotherapy in last 30 years has raised the 5-year survival of these patients to 75 %.[3] On the other hand using chemotherapy before surgery gives us the opportunity of saving the limb in these patients.[4,5] So chemotherapy is now accepted as the standard preoperative option. But the type of chemotherapy is yet in controversy with the majority of regimens, including doxorubicin and cisplatin, with or without high-dose methotrexate (HDMTX, 6 to 12 g/m2 with leucovorin rescue).[6,7,8,9,10] Although methotrexate is used in many centers in combination with cisplatin and doxorubicin as an standard neoadjuvant and adjuvant chemotherapy, its toxicity and nursing care required for exact dose and time of calcium folinate injection has become an important concern for using MTX in centers not specialized for treating such patients. So we tried ifosfamide instead of

MTX and investigated for the necrosis percent and side effects of this chemotherapy regimen. On the other hand we used 24 hour infusion of cisplatin to increase its effect and reduce toxicity.

MATERIALS AND METHODS

15 patients with non-metastatic osteosarcoma, who referred to our center for neoadjuvant chemotherapy since September 2005 to October 2009, were recruited into our study. The range of patients, age was between 17 to 40 years old. The osteosarcoma was diagnosed by bone biopsy. Before chemotherapy function of liver and kidney were checked as well as hematologic profile. Imaging was done for ruling out metastasis. If there was no metastasis or contraindication for chemotherapy, regarding to laboratory tests, the following chemotherapy began for 4 cycles intermittently. After 4 courses done definitive surgery was done and percent of necrosis determined by a single pathologist. The side effects of chemotherapy were recorded. Chemotherapy regimen was doxorubicin and ifosfamide. Doxorubicin 75 mg/m2 administered as one hour continuous infusion. IFO, in combination with an equimolar dose of mesna (800 mg three times a day), was administered as a continuous intravenous infusion (8 g/m2) as a 120-hour continuous infusion, intermittent with of doxorubicin and cisplatin. Cisplatin was infused during 24 hours as a continuous intravenous infusion (100 mg/m2) in combination with doxorubicin (70 mg/m2) in one-hour infusion in three consequent days. Granulocyte colony-stimulating factor was administered after each cycle for 5 days. 9 to 15 weeks after the last cycle of chemotherapy surgery was done. The histological response to primary treatment was assessed in terms of persistence of viable tumor cells or absence of viable tumor cells (total necrosis).

RESULTS

Age of patients was between 15 to 40 years old, 13 males and 2 females. The mean age was 20.1 ± 6.6 years. Tumor necrosis ≥ 90% (defined as good necrosis) was observed in 60% of patients. The mean percent of tumor necrosis was 75.5% ± 31.5%. 69.2% of male patients have good pathologic response (over 90%) and 30.8% of them have poor pathologic response in comparison to female patients who all showed poor pathologic response. Table1 shows the frequency of each pathologic necrosis grade in patients according to the grading system presented by Huvos et al. By this regard, 60% 0f patients have 90% or more necrosis in their pathologic samples.

Table 1: The Frequency of each Pathologic Grade in Patients with Osteosarcoma after Neoadjuvant Chemotherapy

Grade	Number of patients (percent)
Grade I without necrosis	2 (13.3%)
Grade II (50% - 89% necrosis)	4 (26.7%)
Grade III (90% ≤ necrosis <	7 (46.7%)
Grade IV (100% necrosis)	2 (13.3%)

The mean age of patients with good pathologic response was 21.2 ± 7.8 and the mean age of patients with poor pathologic response was 18.5 ± 4.4 years. 3 patients were hospitalized because of the side effects of neoadjuvant chemotherapy. 26.7% of patients showed leucopenia in grade three or four, 26.7% had anemia grade three or four, and 20% thrombocytopenia grade three or four. Mocositis was another side effect of neoadjuvant chemotherapy. Other side effects included: hemorrhagic cystitis in 3 patients, chest pain with T inversion in pericardial electrocardiographic leads in one patient (with normal ejection fraction and cardiac enzymes), and hypokalemia in 2 patients. All these side effects were treated properly without any secondary sequel. There was not any evidence of nephrotoxicity, neurotoxicity, or ototoxicity in any cases.

DISCUSSION

Ferrari S reported 45 % good necrosis in patients treated with drugs (ADM 420 mg/m^2, MTX 120 g/m^2, CDP 600 mg/m^2 and IFO 30 g/m^2)[11] but in our patients good necrosis occurred in 60% of cases .In the Ferrari study there was 4 dead due to toxicity but none of our patients died of chemotherapy .Daw NC in his study reported 60%good necrosis in patient treated with carboplatin, ifosfamide, doxorubicin that is comparable with our study and it is another document for good necrosis without

MTX and even cisplatin.[12] In systemic review done by van Dalen EC there have not been any strong evidences for use of high dose MTX in osteosarcoma and he didn't recommend MTX use in ordinary chemotherapy for patients with osteosarcoma.[13] Besides high dose MTX increase hospitalization and cause serious side effects in patients with excretion.[14, 15] So high dose MTX prescription needs measuring its level and hydration and urine alkalization with laboratory measurements.[14,15,16] In our study good necrosis was less in female but in Collins M study good necrosis was more in females,[17] although our small sample size is a limitation for final conclusion. Kudawara I also showed 66% of good necrosis with chemotherapy regimen including high dose MTX.[18] It is close to our result, But in our study there was not any need for frequent laboratory tests. So use of the above mentioned regimen with lower and predictable toxicity and less laboratory tests can be substituted for high dose MTX with the same percent of good necrosis, but we must consider the sample size for interpreting the final results and our small sample size is limitation of our study.

Considering the results of our study, which revealed less side effects and good necrosis with the new chemotherapy regimen, we suggest that more studies with bigger sample size needs to be done to confirm the new regimen as standard adjuvant chemotherapy for osteosarcoma.

REFERENCES

1. Data from the American Cancer Society file://www.cancer.org/docroot/home/index.asp (Accessed on June 01, 2011).
2. Smith MA, Gurney JG, Ries LA. Cancer in adolescents 15 to 19 years old. In: Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995 (Pub #99-4649), Ries LA, Smith MAS, Gurney JG, et al (Eds), SEER program, National Cancer Institute, Bethesda, MD 1999.
3. Anninga JK, Gelderblom H, Fiocco M, et al. Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? Eur J Cancer 2011; 47:2431.
4. Rosen G. Preoperative (neoadjuvant) chemotherapy for osteogenic sarcoma: a ten year experience. Orthopedics 1985; 8:659.
5. Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology Group Study POG-8651. J Clin Oncol 2003; 21:1574.
6. Eilber F, Giuliano A, Eckardt J, et al. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol 1987; 5:21.
7. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986; 314:1600.
8. Link MP, Goorin AM, Horowitz M, et al. Adjuvant chemotherapy of high-grade osteosarcoma of the extremity. Updated results of the Multi-Institutional Osteosarcoma Study. Clin Orthop Relat Res 1991; :8
9. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000; 18:4016.
10. Schwartz CL, Wexler LH, Devidas M, et al. P9754 therapeutic intensification in non-metastatic osteosarcoma: a COG trial (abstract). Proc Am Soc Clin Oncol 2004; 23:798a
11. Ferrari S, Ruggieri P, Cefalo G, Tamburini A, Capanna R, Fagioli F, Comandone A, Bertulli R, Bisogno G, Palmerini E, Alberghini M, Parafioriti A, Linari A, Picci P, Bacci G.Neoadjuvant chemotherapy with methotrexate, cisplatin, and doxorubicin with or without ifosfamide in nonmetastatic osteosarcoma of the extremity: an Italian sarcoma group trial ISG/OS. J Clin Oncol. 2012 Jun 10;30(17):2112-8. doi: 10.1200/JCO.2011.38.4420..
12. Daw NC, Neel MD, Rao BN, Billups CA, Wu J, Jenkins JJ, Quintana J, Luchtman-Jones L, Villarroel M, Santana VM.Frontline treatment of localized osteosarcoma without methotrexate: results of the St. Jude Children's Research Hospital OS99 trial . Cancer. 2011 Jun 15; 117(12):2770-8. doi: 10.1002/cncr.25715.
13. Van Dalen EC, van As JW, de Camargo B. Methotrexate for high-grade osteosarcoma in children and young adults . Cochrane Database Syst Rev. 2011 May 11 ;(5):CD006325.
14. Holmboe L, Andersen AM, Mørkrid L, Slørdal L, Hall KS. High dose methotrexate chemotherapy: pharmacokinetics, folate and toxicity in osteosarcoma patients. Br J Clin Pharmacol. 2012 Jan; 73(1):106-14.
15. Lee KM, Lee HW, Kim SY, Lee HJ, Kim DH, Cho J, Kim DH, Lim JS, Lee JK, Lee JA. Two pediatric

osteosarcoma cases with delayed methotrexate excretion: its clinical course and management. Cancer Res Treat. 2011 Mar; 43(1):67-70. doi: 10.4143/crt.2011.43.1.67.

16. Mahadeo KM, Santizo R, Baker L, Curry JO, Gorlick R, Levy AS. Ambulatory high-dose methotrexate administration among pediatric osteosarcoma patients in an urban, underserved setting is feasible, safe, and cost-effective. Pediatr Blood Cancer. 2010 Dec 15;55(7):1296-9. doi: 10.1002/pbc.22772.
17. Collins M, Wilhelm M, Conyers R, Herschtal A, Whelan J, Bielack S, Kager L, Kühne T, Sydes M, Gelderblom H, Ferrari S, Picci P, Smeland S, Eriksson M, Petrilli AS, Bleyer A, Thomas DM. Benefits and adverse events in younger versus older patients receiving neoadjuvant chemotherapy for osteosarcoma: findings from a meta-analysis. J Clin Oncol. 2013 Jun 20; 31(18):2303-12. doi: 10.1200/JCO.2012.43.8598.
18. Kudawara I, Aoki Y, Ueda T, Araki N, Naka N, Nakanishi H, Matsumine A, Ieguchi M, Mori S, Myoui A, Kuratsu S, Hashimoto N, Yoshikawa H. Neoadjuvant and adjuvant chemotherapy with high-dose ifosfamide, doxorubicin, cisplatin and high-dose methotrexate in non-metastatic osteosarcoma of the extremities: a phase II trial in Japan. J Chemother. 2013 Feb; 25(1):41-8.